



RESEARCH ARTICLE

Estimating the duration of seropositivity of human seasonal coronaviruses using seroprevalence studies [version 1; peer review: 1 approved, 2 approved with reservations]

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V1 First published: 03 Jun 2021, 6:138
<https://doi.org/10.12688/wellcomeopenres.16701.1>
Latest published: 03 Jun 2021, 6:138
<https://doi.org/10.12688/wellcomeopenres.16701.1>

Abstract

Background: The duration of immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still uncertain, but it is of key clinical and epidemiological importance. Seasonal human coronaviruses (HCoV) have been circulating for longer and, therefore, may offer insights into the long-term dynamics of reinfection for such viruses.

Methods: Combining historical seroprevalence data from five studies covering the four circulating HCoVs with an age-structured reverse catalytic model, we estimated the likely duration of seropositivity following seroconversion.

Results: We estimated that antibody persistence lasted between 0.9 (95% Credible interval: 0.6 - 1.6) and 3.8 (95% CrI: 2.0 - 7.4) years. Furthermore, we found the force of infection in older children and adults (those over 8.5 [95% CrI: 7.5 - 9.9] years) to be higher compared with young children in the majority of studies.

Conclusions: These estimates of endemic HCoV dynamics could provide an indication of the future long-term infection and reinfection patterns of SARS-CoV-2.

Keywords

Seasonal coronavirus, Seroprevalence, Catalytic model, waning immunity

Open Peer Review

Reviewer Status ? ✓ ?

	Invited Reviewers		
	1	2	3
version 1	?	✓	?
03 Jun 2021	report	report	report

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Competing interests: No competing interests were disclosed.

Grant information: AK was supported by Wellcome Trust and the Royal Society (grant Number 206250/Z/17/Z). EMR receives funding from the UK Medical Research Council (MR/N013638/1). NRW receives funding from the UK Medical Research Council (MR/N013638/1). RL was supported by a Royal Society Dorothy Hodgkin Fellowship.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Rees EM, Waterlow NR, Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group *et al.* **Estimating the duration of seropositivity of human seasonal coronaviruses using seroprevalence studies [version 1; peer review: 1 approved, 2 approved with reservations]** Wellcome Open Research 2021, 6:138 <https://doi.org/10.12688/wellcomeopenres.16701.1>

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel beta coronavirus, was first detected in December 2019 and has since spread globally causing high morbidity and mortality. There is evidence of some short-term sterilising immunity (protection against reinfection and symptoms) following infection with SARS-CoV-2¹, but also some reports of reinfection². However, there is currently limited evidence on the duration of immunity conferred by SARS-CoV-2 infection. Given the limited duration of SARS-CoV-2 circulation to date, the dynamics of antibody responses of seasonal human coronaviruses (HCoV) could provide insights into the possible long-term potential for reinfections³. The duration of immunity following infection is of both clinical and epidemiological importance, as it provides information as to how long previously infected individuals may no longer be at risk of infection and disease, as well as influencing the long-term dynamics of epidemics⁴ and enabling the interpretation of population-wide serological data⁵.

There are four circulating HCoVs: HCoV-NL63 and HCoV-229E (alpha coronaviruses), HCoV-OC43 and HCoV-HKU1 (beta coronaviruses). HCoV-OC43 and HCoV-229E were first identified in the 1960s, but HCoV-NL63 and HCoV-HKU1 were not identified until 2004 and 2005 respectively^{6,7}. Like SARS-CoV-2, these typically cause respiratory tract infections. A small number of human challenge studies have looked at the duration of immunity to these viruses. Callow *et al.*⁸ found that six out of nine participants were reinfected when challenged with HCoV-229E again one year later, as measured by a rise in IgG antibodies and viral shedding. However, the period of viral shedding was shorter following the second inoculation, and none of the participants developed symptoms. Reed⁹ found that reinfection did not occur when participants were re-inoculated with a homologous strain approximately one year following infection, but participants had partial immunity against reinfection with a heterologous strain. Taken together these results suggest that immunity against infection with a homologous strain could last at least one year^{8,9}.

There are also a small number of cohort and community-based surveillance studies which have looked at reinfection of seasonal HCoV. One study looked at HCoV reinfection in a small cohort of ten individuals over 35 years and found the median reinfection times to be 30 months, but with reinfection often occurring at 12 months¹⁰. A larger study looking at data from Flu Watch, a community cohort study which measures the incidence and transmission of respiratory viruses, found that between 2006 and 2011, eight subjects were reinfected with a seasonal HCoV (of 216 with confirmed first infection), and the time between reinfection ranged from 7 to 56 weeks. None of these reinfections were with the same strain, providing some evidence of lasting immunity¹¹. However, a community surveillance study conducted in Kenya in 2010 over six months found evidence of high numbers of repeat infections of HCoV-NL63 (20.9%), HCoV-OC43 (5.7%), and HCoV-229E (4.0%). The majority of these reinfections showed reduced virus replication in the second infection, and a lower proportion of individuals had symptoms following the second infection¹².

Furthermore, another study conducted in New York City found that reinfections with the same strain can occur within one year¹³. Care should be taken with the interpretation of these studies since we do not know the background exposure rates, and this will influence the estimates of duration of immunity.

If infections are fully immunising – as is the case for pathogens like measles, pertussis and varicella zoster – then seroprevalence would be expected to accumulate over time¹⁴, and hence with age, with little waning of responses. The dynamics can therefore be captured with catalytic models of seroconversion¹⁵, which enables estimation of the force of infection (FOI, the rate at which susceptible individuals acquire infection and seroconvert). In contrast, when individuals serorevert, i.e. their immunity wanes by the progressive loss of protective antibodies against a disease over time, ‘reverse catalytic models’ can jointly estimate FOI and waning of immunity¹⁶. Variation in FOI with age may further complicate the dynamics, particularly if a high infection rate in children is followed by a lower rate in adults as well as waning of seroprevalence. To understand how seroconversion, waning and age-variation in infection risk could shape population-level seroprevalence, we combine age-stratified data with age-structured reverse catalytic models, and estimate the likely duration of seropositivity following seroconversion for the four seasonal coronaviruses.

Methods

Human seroprevalence from four different human coronavirus strains (229E, HKU1, NL63, and OC43) were identified in a recent systematic review⁷. Studies which did not include estimates for individuals under 10 years old¹⁷ were excluded, as well as studies with a small number of data points¹⁸. A total of six different studies were included, covering the four seasonal HCoVs, with some studies reporting on multiple strains^{19–24}. Two studies were reported separately for two different strains, but the overall study population was the same^{21,22}. A summary of these studies is presented in Table 1. The different assays used in each study for the different strains is shown, and where the antibody detected was specified this is included in the table. To account for maternal immunity individuals aged ≤ 1 year were excluded. The full dataset used for this analysis can be found as underlying data²⁵.

To explore the duration of antibody persistence for different seasonal coronaviruses, where detectable antibodies is defined as seropositivity, we developed age-structured reverse catalytic models. The basic reverse catalytic model follows individuals from birth and assumes that there is a constant FOI (λ), which is independent of age (a) and calendar year, and that immunity (as measured by serological status) wanes over time, at a rate ω . This model also assumes that the mortality rate for susceptible and infectious individuals is the same. The expression for the proportion of individuals age a who are seropositive, $z(a)$, in the reverse catalytic model is as follows:

$$z(a) = \frac{\lambda}{\lambda + \omega} (1 - e^{-a(\lambda + \omega)})$$

where λ is the FOI, ω is immunity waning rate and a is age.

Table 1. Characteristics of studies used to fit the model.

Strain	Author (year published)	Pubmed ID	Sample size	Country/region	Years sampled	Assay
HCoV-HKU1	Chan (2009)	19342289	709	Hong Kong	Not specified	ELISA (IgG)
	Zhou (2013) ^a	24040960	789	China	1999 – 2011	IFA (IgG)
HCoV-OC43	Zhou (2013) ^a	24040960	789	China	1999 – 2011	IFA (IgG)
	Monto (1974) ^c	4816305	910	USA	1965 – 1969	CF or HAI
	Sarateanu (1980)	6248465	3,016	Germany	1974 – 1976	HI
HCoV-NL63	Shao (2007) ^b	17889596	243	USA	2003 – 2004	ELISA (IgG)
	Zhou (2013) ^a	24040960	789	China	1999 – 2011	IFA (IgG)
HCoV-229E	Shao (2007) ^b	17889596	243	USA	2003 – 2004	ELISA (IgG)
	Zhou (2013) ^a	24040960	789	China	1999 – 2011	IFA (IgG)
	Cavallaro (1970) ^c	5504709	307	USA	1965	Neutralization

Enzyme-linked immunosorbent assays (ELISA), immunofluorescence assays (IFA), western blots, complement fixation (CF), hemagglutination inhibition assays (HAI). Studies which occurred in the same setting are denoted by the superscripts, ^a, ^b and ^c.

We then extended the reverse catalytic model to allow for a different FOI by age. The expressions for seroprevalence in the reverse catalytic model with age-varying FOI are as follows:

$$z(a) = \frac{\lambda_1}{\lambda_1 + \omega} (1 - e^{-a(\lambda_1 + \omega)}) \quad \text{when } a < a_0$$

$$z(a) = \left(\frac{\lambda_1}{\lambda_1 + \omega} (1 - e^{-a_0(\lambda_1 + \omega)}) - \frac{\lambda_2}{\lambda_2 + \omega} (e^{-(\lambda_2 + \omega)(a - a_0)}) \right) + \frac{\lambda_2}{\lambda_2 + \omega} \quad \text{when } a \geq a_0$$

$$\lambda_2 = \lambda_1 \alpha$$

Where $z(a)$ is those who are seropositive at age a , λ_1 is the FOI in young age groups, λ_2 is FOI in the old age group, ω is waning, a is age, a_0 is the age cut-off used to define the young and old group, and the relative change in FOI, α , is the change in FOI in the older age group. In our analysis, we allowed λ_1 to vary by study and strain, to account for local differences in population-level transmission dynamics, while the average rate of waning within a given individual was assumed to be universal and was jointly estimated across all studies and strains. This means that one overall estimate of waning was obtained. Some of the studies occurred in the same setting, and so the underlying contact patterns were presumed to be the same (in total we identified five settings). Therefore, the relative change in FOI (α) and the age at cut-off (a_0) were jointly estimated across settings. This model assumes no cross-protection between strains. Annual attack rates were calculated after estimating the FOI using the following expression,

$$\text{Attack rate} = 1 - e^{-\lambda}.$$

To reflect uncertainty in current knowledge about the transmission dynamics of HCoVs, weakly informative distributions were

chosen as priors for ω , the rate of waning over time, and a_0 , the age at the cut-off time. Specifically, uniform priors from 0 to 5 and 0 to 20 years, respectively, were chosen as we were interested in the change in FOI in children and young adults. For FOI, a Gamma distribution, parameterised using plausible attack rates of HCoV, with a mean of 0.3 (corresponding to an attack rate of 26%) was chosen (shape = 1.2 and scale = 0.25). There is little information on the attack rate of HCoVs, but there have been several systematic reviews and meta-analyses looking at unvaccinated individuals which have reported the attack rate to range between 15.2% – 22.5% in children and 3.5% – 10.7% in adults^{26–28}. Modelling studies using serological influenza data predicted estimates from 20 – 60%^{29,30}. We expect the attack rate for HCoV may be lower based on the epidemiology of these viruses in children³¹, but we selected a prior which covers a range of plausible values. For the relative change in FOI (α) we did not have any prior information. Therefore, we selected a prior with median 1, which presumes no difference between FOI in young compared with FOI in old and allowed for a range of plausible values using a gamma distribution (shape = 5, scale = 0.2).

Several sensitivity analyses were conducted to assess the robustness of these results. Firstly, the choice of priors for the FOI was explored, and a less informed prior was tested (FOI ~ Normal (mean 0.3, standard deviation 0.5)). Secondly, waning was estimated by strain, instead of being jointly fitted across all studies. Thirdly, the relative change in FOI (α) and age at cut-off (a_0) were held across all studies (instead of allowing them to vary by setting) to explore the impact on the estimate for waning. The impact of excluding the youngest age groups (≤ 1 year) was also explored, and a model was run which included individuals ≤ 1 year. Finally, the primary model (age-varying

FOI model) was fitted using only half the data (seroprevalence studies from two strains), to explore whether the results from one study was heavily influencing the results. For this model, waning, the relative change in FOI (α) and age at cut-off (a_0) were held across all studies. A description of these models is presented in [Table 2](#).

Bayesian inference was used to fit the sero-catalytic models to the seroprevalence data, using Markov chain Monte Carlo (MCMC) with the Gibbs sampling algorithm to estimate model parameters. To do so, we used the following binomial likelihood representing seropositivity by age (a), study (i) and strain (j)

$$y_{ija} \sim \text{Binomial}(P_{ija}, N_{ija}),$$

where N_{ija} is total number of individuals by age group, strain and study, and P_{ija} is the proportion of individuals who are seropositive. The inference was implemented in [RJags](#) (version 4–10)³². The Gelman-Rubin statistic was used to evaluate MCMC convergence, and a threshold of <1.1 was chosen. The effective sample size (ESS), which is the estimated number of independent samples accounting for autocorrelations generated by the MCMC run, was checked, and an ESS >200 was used. All analysis and calculations were performed

using [R](#) version 3.6.1. Model selection was based on the lowest value of the deviance information criterion (DIC). All code is available here at [GitHub](#)²⁵.

Results

Using a reverse catalytic model, which allowed the FOI to change in individuals by age, we estimated the duration of antibody persistence for the four seasonal HCoV²⁵. Despite having only four parameters by study, our model could capture the overall trends in most studies ([Figure 1](#)). Waning was jointly fitted across all studies and strains to obtain one overall estimate, and the duration of antibody persistence was estimated to be 3.75 (95% credible interval [CrI]: 1.96 - 7.38) years ([Table 3](#)). The FOI across all studies and strains in the young age group ranged from 0.02 (95% CrI: 0.01 - 0.05) to 1.06 (95% CrI: 0.57 - 1.68). The cut-off (age at which the FOI changes) ranged between 2.35 (95% CrI: 0.31 - 17.51) to 16.58 (95% CrI: 7.71 - 19.81) years. The relative change in FOI (Alpha) which measures the relative value of FOI in the young age group compared with the older age group ranged from 0.72 (95% CrI: 0.3 - 1.17) to 2.48 (95% CrI: 1.96 - 2.99). For three of the study settings, the FOI in the older age group was higher ([Figure 2](#)). A sensitivity analysis was conducted using less informative priors for the FOI parameters, where a

Table 2. Description of models explored.

Model	Priors	Number of parameters
Main model: Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings) - More informed priors	FOI ~ gamma(shape = 1.2, scale = 0.25) Waning ~ uniform(0,5) Alpha ~ gamma(shape = 5, scale = 0.2) Cut-off ~ uniform(0,20)	21
Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings) - less informed priors	FOI ~ normal(0.3,0.5) Waning ~ uniform(0,5) Alpha ~ gamma(shape = 5, scale = 0.2) Cut-off ~ uniform(0,20)	21
Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings, waning varying by strain)	FOI ~ gamma(shape = 1.2, scale = 0.25) Waning ~ uniform(0,5) Alpha ~ gamma(shape = 5, scale = 0.2) Cut-off ~ uniform(0,20)	24
Reverse catalytic model with age-varying FOI (alpha and cut-off held across settings)	FOI ~ gamma(shape = 1.2, scale = 0.25) Waning ~ uniform(0,5) Alpha ~ gamma(shape = 5, scale = 0.2) Cut-off ~ uniform(0,20)	13
Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings) using all data	FOI ~ gamma(shape = 1.2, scale = 0.25) Waning ~ uniform(0,5) Alpha ~ gamma(shape = 5, scale = 0.2) Cut-off ~ uniform(0,20)	21
Reverse catalytic model	FOI ~ gamma(shape = 1.2, scale = 0.25) Waning ~ uniform(0,5)	11

Alpha (α), the relative change in FOI; Cut-off (a_0), the age at cut-off.

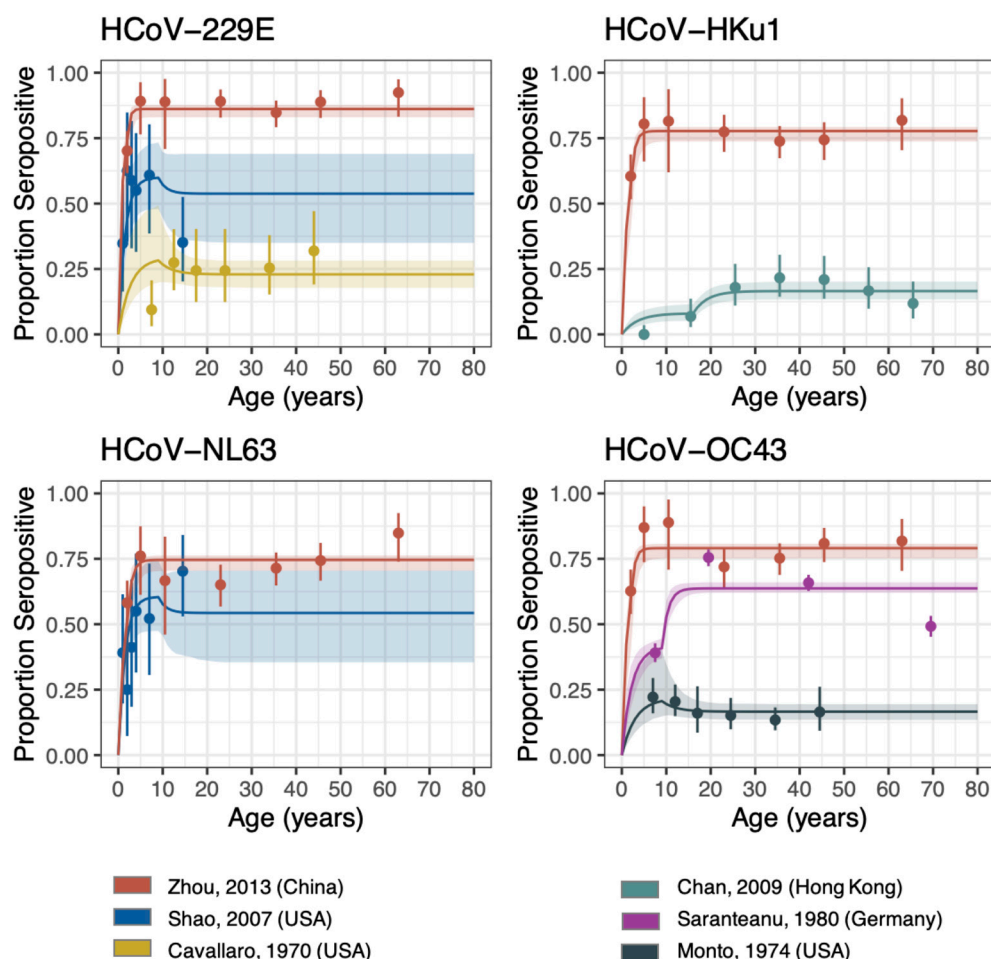


Figure 1. Reverse catalytic model with age-varying FOI. The points are the observed proportion of seropositive individuals from each study (with confidence intervals), i.e. the data that was fit to. The lines are the seroprevalence curves, sampled from the fitted model, where the shaded region represents the 95% credible interval of the predictive posterior distribution. FOI was allowed to vary by study, whilst the relative change in FOI (Alpha) and cut-off were allowed to vary by setting. Waning was jointly fit across all studies and strains.

normal distribution was used (extended data Figure 1, Table 1³³). This model estimated a shorter duration of antibody persistence [0.93 (95% CrI: 0.60 - 1.64) years]. The FOI across all studies and strains were higher, ranging from 0.09 (95% CrI: 0.04 - 0.16) to 3.22 (95% CrI: 1.95 - 4.85), with six studies reporting FOI estimates > one, which is equivalent to an attack rate of >63%. The relative change in FOI and cut-off were similar for both models. This model had a lower DIC (476.8 compared with 480.8; Table 4), with a DIC difference of 4, however, the high FOI estimates indicate that this model may be less plausible. As an additional sensitivity we allowed the waning estimate to vary by strain (extended data Table 2³³). This model estimated the duration of immunity to be similar for all strains, ranging from 2.26 (1.06 - 5.07) years for HCoV-OC43 to 4.09 (1.91 - 9.60) years for HCoV-229E.

When the relative change in FOI and cut-off parameters were simultaneously estimated by setting (extended data Figure 2, Table 3³³) the duration of antibody persistence was estimated to be shorter, 2.20 (95% CrI: 1.57 - 3.08) years, although the confidence intervals overlap with the main model. The FOI ranged from 0.04 (95% CrI: 0.03 - 0.06) to 0.88 (95% CrI: 0.67 - 1.19). The overall model DIC was higher (548.2 compared with 480.8; Table 4), indicating that this model did not have as much support.

We also tested a basic reverse catalytic model, where the FOI was not allowed to vary by age, and this model estimated a longer duration of antibody persistence (7.69 [95% CrI: 6.25 - 9.09] years; extended data Table 4, Figure 3³³). The DIC value for the basic reverse catalytic model was higher, (608.3

Table 3. Parameter estimates from the age-varying FOI reverse catalytic model (median [95% CrI]). FOI was allowed to vary across study, while waning was simultaneously estimated across all studies. The relative change in FOI (Alpha) and the cut-off were allowed to vary across study settings.

Strain	First Author	FOI	Relative change in FOI (Alpha)	Cut-off	Waning
HCoV-229E	Shao	1.06 (0.57 – 1.68)	0.78 (0.35 – 1.68)	9.5 (0.59 – 19.47)	0.27 (0.14 – 0.51)
	Zhou	0.11 (0.06 – 0.3)	1.57 (0.8 – 2.65)	2.35 (0.31 – 17.51)	
	Cavallaro	0.02 (0.01 – 0.05)	0.72 (0.3 – 1.17)	9.14 (0.57 – 19.28)	
HCoV-HKU1	Chan	0.59 (0.32 – 0.89)	2.27 (1.44 – 3.45)	16.58 (7.71 – 19.81)	
	Zhou	0.64 (0.35 – 0.96)	1.57 (0.8 – 2.65)	2.35 (0.31 – 17.51)	
HCoV-OC43	Zhou	0.07 (0.04 – 0.19)	1.57 (0.8 – 2.65)	2.35 (0.31 – 17.51)	
	Monto	0.19 (0.11 – 0.35)	0.72 (0.3 – 1.17)	9.14 (0.57 – 19.28)	
	Saranteanu	0.5 (0.27 – 0.74)	2.48 (1.96 – 2.99)	9.93 (7.34 – 14.84)	
HCoV-NL63	Zhou	0.41 (0.26 – 0.67)	1.57 (0.8 – 2.65)	2.35 (0.31 – 17.51)	
	Shao	1.06 (0.57 – 1.68)	0.78 (0.35 – 1.68)	9.5 (0.59 – 19.47)	

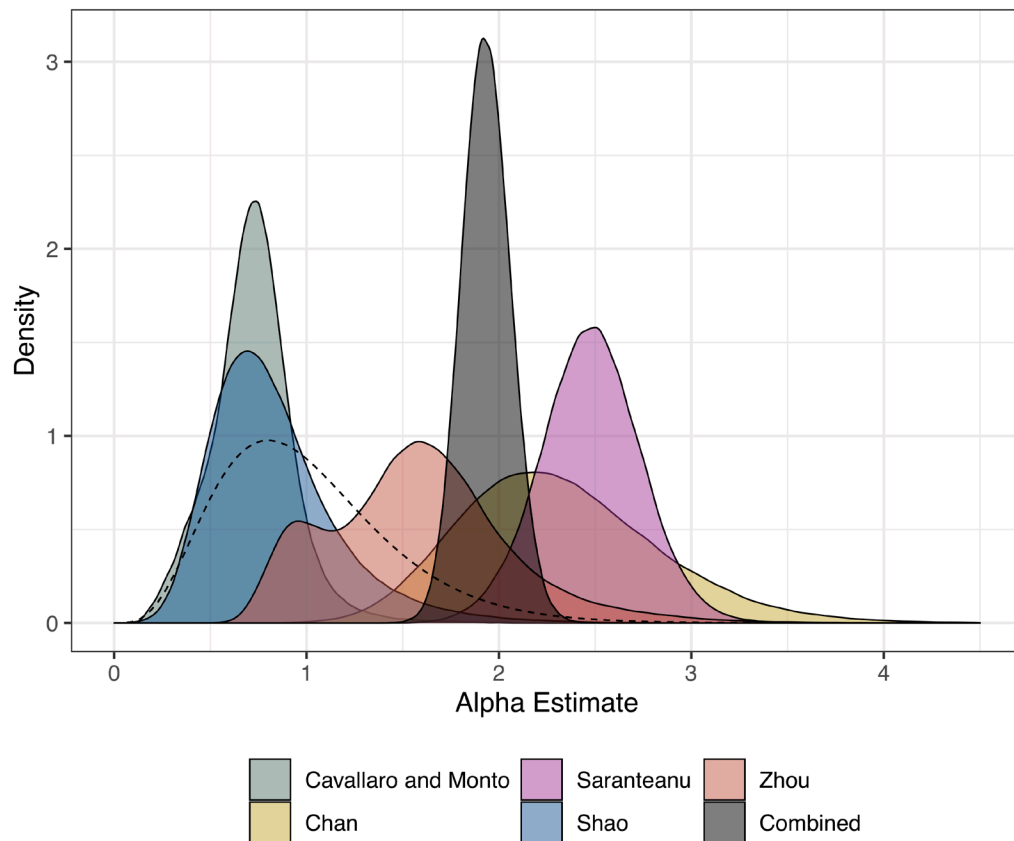


Figure 2. Posterior estimates for the relative change in FOI (alpha) from the age-varying reverse catalytic model for each study setting. The alpha estimate from the model where alpha and cut-off were simultaneously estimated across studies is shown in grey as “combined”. The prior is shown as a dashed line.

compared with 480.8) indicating that this basic model did not have strong support among the models considered (Table 4).

To explore the effect of excluding the youngest ages (≤ 1 year), a sensitivity analysis was done where these individuals were included within the analysis. The duration of antibody persistence was found to be slightly shorter (2.04 [95% CrI: 0.128 - 1.476] years) and the FOI was found to be higher for all studies, ranging from 0.04 (95% CrI: 0.02 - 0.07) to 2.92 (95% CrI: 2.08 - 4.01); extended data Table 5, Figure 4³³). The estimates for the relative change in FOI were found to be very similar to the model which excluded this age group.

As an additional sensitivity analysis, we refit the models using data for only two strains at a time, and estimated the FOI, waning and the relative change in FOI (extended data Table 6³³).

We found that although the results varied, the overall trends were the same, indicating that the model did not rely heavily on one dataset. The waning estimates varied from 1.80 years (95% CrI: 1.17 - 2.67) to 5.26 years (95% CrI: 2.53 - 13.56).

Using the parameters for the relative change in FOI and waning estimated from the age-varying reverse catalytic model where the relative change in FOI and the age at cut-off were simultaneously estimated across settings, we simulated the proportion of individuals aged 30 years that would be seropositive using a range of FOI estimates to show how the proportion changes using the different models (Figure 3A). We also used the pooled estimate across all studies of FOI to estimate the proportion exposed at a given age to provide an indication of how many infections we might expect to see by age (Figure 3B).

Table 4. Comparison of duration of antibody persistence estimates from the different models explored.

Model	Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings) - More informed priors	Reverse catalytic model with age-varying FOI (alpha and cut-off varying across settings) - less informed priors	Reverse catalytic model with age-varying FOI (alpha and cut-off held across settings)	Reverse catalytic model
Duration of antibody persistence (years)	3.75 (1.96 - 7.38)	0.93 (0.60 - 1.64)	2.20 (1.57 - 3.08)	7.69 (6.25 - 9.09)
DIC	480.8	476.8	548.2	608.3

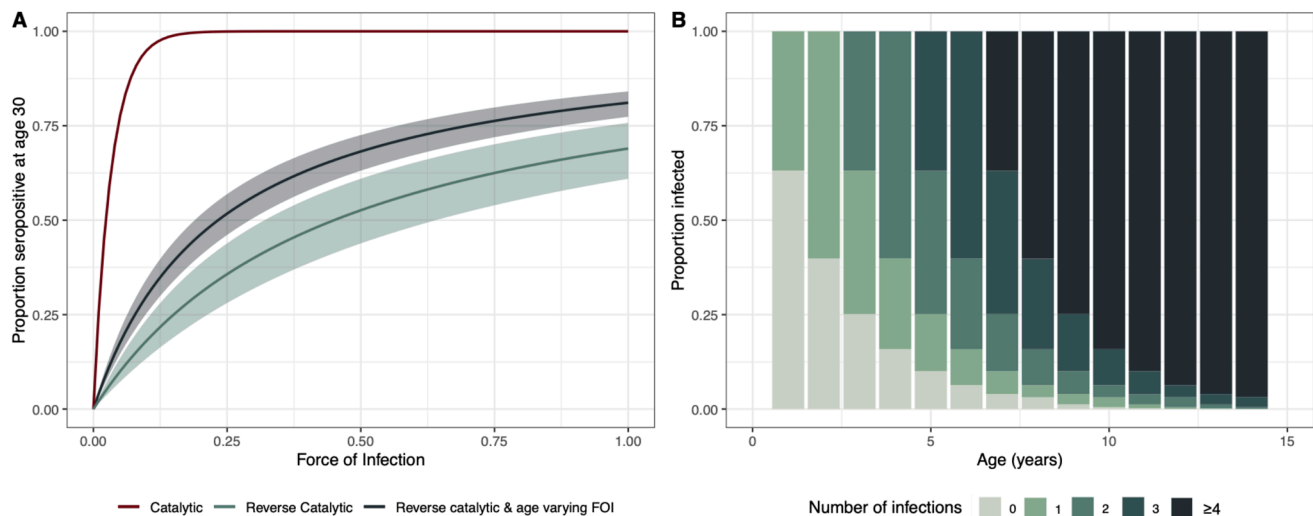


Figure 3. (A) Proportion of individuals age 30 who are seropositive for different estimates of force of infection (FOI). The catalytic model is shown in red, the reverse catalytic model in green, and the reverse catalytic model with time-varying FOI is shown in blue. Model estimates were used for the parameter values (relative change in FOI (alpha), 1.93 [1.69 - 2.19]; waning, 0.45 [0.32 - 0.64]; cut-off, 8.49 [7.52 - 9.94]). **(B)** Estimated proportion of individuals experiencing infections by age, using the pooled median estimate across studies for FOI (0.46), and median estimates for waning (0.45), alpha (1.93) and cut-off (8.49).

Discussion

To date, there has been limited evidence about the duration of immunity to SARS-CoV-2. Given the inevitable right censoring of data during an emerging infectious disease pandemic, understanding the duration of protection following infection with HCoV could help provide insights which will be relevant to SARS-CoV-2. Using an age-varying reverse catalytic model, we estimated the overall duration of immunity, as measured by seropositivity, to be between 0.9 (95% CrI: 0.6 - 1.6) years and 3.8 (95% CrI: 2.0 - 7.4) years for HCoV's. When waning was estimated by strain, we found comparable estimates of the duration of seropositivity, indicating that the assumption that waning is similar across strains holds true. Previous studies have produced varied estimates for the duration of immunity for HCoVs. One study estimated the median duration of immunity to be 2.5 years¹⁰, and Reed found immunity lasts at least one year⁹. However, several studies have reported reinfection occurring in less than one year^{8,11–13}. Aldridge *et al.*¹¹ found that reinfection with HCoV did not occur with the same strain, but Kiyuka *et al.*¹² found reinfection frequently occurred with the same strain within a six month period. The reverse catalytic model assumes that waning occurs at a constant rate, however, individuals may become reinfected within a shorter time period than average, and conversely some will take longer. Some evidence also exists for the duration of immunity to SARS-CoV-2. A recent survey of health care workers in Oxford, UK, found that protection against reinfection with SARS-CoV-2 lasts at least six months³⁴, whilst another study of health care workers from across the UK conducted by Public Health England found that immunity lasts for at least five months². This seems to align with what is known about reinfection in seasonal HCoVs. However, these studies only followed up individuals for six months and five months respectively, and longer follow-up times are needed. Future studies could also work to untangle the relationship between seroreversion as a result of waning homotypic antibody responses and antigenic evolution leading to a mismatch between prior immunity and circulating viruses³³.

More informed priors for the FOI based on attack rates for influenza, resulted in higher estimates for the duration of seropositivity. When we used less informed priors for the FOI, a lower estimate of duration of seropositivity was obtained. However, this model produced higher estimates of FOI, with six studies reported FOI estimates in the young age group greater than one (attack rate >63%). There is limited information on the attack rate of seasonal HCoV, however there have been numerous studies looking at influenza. Previous systematic reviews have estimated the attack rate of influenza to be between 3.5% and 22.5%^{26–28}, whilst modelling studies have estimated this to be higher, 20 – 60%^{29,30}. Based on reporting rates of seasonal HCoV we would expect the attack rate to be lower than influenza. Therefore, this suggests that the results from the model with less informative priors are less plausible. Maternally derived immunity may also have a role, protecting young infants from infection. We tested this with a model which included individuals ≤ 1 year. This resulted in a shorter estimate of the duration of antibody persistence,

and a higher FOI, suggesting that maternal immunity may be important.

A wide range of different assays were used in the studies we considered in our analysis, including enzyme-linked immunosorbent assays (ELISA), immunofluorescence assays (IFA), western blots, and complement fixation (CF), hemagglutination inhibition assays (HAI) and neutralisation assays. Neutralisation assays are considered to be the gold standard as they measure the ability of the sera to inhibit viral processes³⁶. Only Cavallaro and Monto²² used a neutralisation assay. Other assays, such as ELISA and IFA, do not assess the functionality of the antigen, but instead detect the presence of antibodies in a sample. Zhou *et al.*¹⁹ and Chan *et al.*²³ used IFA to detect levels of IgG antibodies. A recent study provided evidence that IgG antibodies in SARS-CoV-2 are correlated with neutralising antibodies, and may therefore act as a correlate of sterilising immunity³⁷, whilst another study suggested that neutralizing antibodies may be correlated with protection against reinfection¹. Therefore, although antibody prevalence does not equate to immunity for seasonal HCoVs, prevalence of IgG antibody may be a good correlate of immunity. However, all of these assays only assess humoral immunity, and it is thought that cellular immunity also has a role SARS-CoV-2, and so it is likely to be also important in seasonal HCoVs^{38–40}.

The seroprevalence surveys included in this study were conducted in different countries and settings (USA, China, Germany and Hong Kong), as well as in different time-periods (ranging from 1965–2011). It is likely that there are differences in social structure and contact patterns between these settings. Furthermore, individual level data was not available for these studies, and instead aggregated data was used. Finer resolution, particularly for the younger age groups, would have helped to provide more certainty with these estimates. In addition, we did not take into consideration cross protection between seasonal coronavirus strains. There is also some evidence that there is cross-reactivity with different coronaviruses, which may lead to false positive results. A recent systematic review found that there was some cross-reactivity that occurred within alpha (HCoV-229E and HCoV-NL63) and beta (HCoV-OC43 and HCoV-HKU1) coronaviruses, but minimal reactivity between alpha and beta coronaviruses⁷. However, it is not clear whether cross-reactivity equates to cross-protection. We also did not account for seasonality within this model, which may have under-estimated our FOI. Whitaker & Farrington⁴¹ found that accounting for seasonality resulting from past epidemics only had a marginal effect on the estimates, and that regular epidemic dynamics do not strongly bias the catalytic model. On the other hand, Ferrari *et al.*⁴² found that ignoring seasonality may overemphasize the role of adults in the transmission. We also assume an overall FOI by age, and we do not account for differences in population susceptibility, for example health care workers or immunocompromised individuals. Despite these limitations, the duration of immunity estimated in this study is in line with literature estimates, suggesting the age-varying reverse catalytic model was able to capture overall dynamics.

Numerous studies have looked at the age pattern of HCoV patients presenting to hospital and healthcare settings, and predominantly found that the burden of disease is higher in younger children and the elderly^{43–45}. However, it is likely that these age groups may have more severe symptoms and are therefore more likely to be reported. In contrast, seroprevalence data makes it possible to examine the whole population for evidence of past exposure, and hence can provide a clearer understanding of the underlying transmission dynamics of disease, rather than just the resulting burden.

In this study, when the relative change in FOI and the age of cut-off were simultaneously estimated across studies, we found that the FOI was estimated to be twice as high in the older age group (in this case, those over 8.49 [CrI: 7.52 - 9.94] years), compared with the younger age group. A similar pattern was observed for three of five datasets when the relative change in FOI and the cut-off age were allowed to vary by setting. This suggests that older children and adults may be important for the transmission of seasonal HCoVs in some settings. A previous study looking at social mixing patterns in Europe⁴⁶ found that children are expected to have the highest incidence during the initial stages of an epidemic as a result of their social mixing patterns, and this is what is found for some diseases, such as seasonal influenza, where there is evidence young children drive transmission^{47,48}. However, a more recent study looking at a large scale dataset of movement and contact patterns in the United Kingdom data found contact intensity was highest in the 18–30 year age group when looking at all types of contacts (conversational, which was defined as face-to-face conversation of three or more words, and physical), although for physical alone, those aged 5–9 years had the highest contact⁴⁹. Therefore, any association between contact intensity and transmission will depend on the contacts considered, particularly if a pathogen is more commonly spread via conversational contacts or via prolonged physical contacts. One possible explanation for the higher FOI we estimate in older age groups is that conversational contacts – which are typically higher in volume but lower in duration and intensity – could be more important for the transmission of seasonal HCoVs.

The results from this study are in accordance with what studies have observed in children during the coronavirus disease 2019 (COVID-19) pandemic, with low numbers of cases reported in young age groups, and several large seroprevalence studies have reported lower seroprevalence in children compared with adults^{50,51}. As well as differences in contact structure, this could be explained in part by reduced susceptibility to acquisition of infection, and a meta-analysis of contact tracing studies found that children had 56% (31% – 71%) lower odds of becoming an infected contact compared with adults⁵².

The duration of immunity to SARS-CoV-2 is still largely unknown and is of significance for the interpretation of population wide serological data, the understanding of the long-term dynamics of the epidemic, as well as of clinical importance. Given the long-term circulation of seasonal HCoVs, data on these related coronaviruses could provide indications of the

possible future dynamics of SARS-CoV-2. With infection likely to become endemic in parts of the world, the duration of antibody-mediated immune responses will be particularly important in shaping transmission patterns in years to come. Using seroprevalence data, in this study we estimated the duration of seropositivity to seasonal HCoVs following seroconversion to be between 0.9 (95% CrI: 0.6 - 1.6) years and 3.8 (95% CrI: 2.0 - 7.4) years. We allowed the FOI to vary by age group and found it to be lower in young children (≤ 8.5 years) compared with older children and adults, which is corroborated with what has been observed in the COVID-19 pandemic. This suggests individuals in settings with endemic HCoVs accumulate multiple infections over the course of their lifetime, punctuated by periods of waning seropositivity against circulating viruses.

Data availability statement

Underlying data

Zenodo: erees/seasonalHCoV: First release. <https://doi.org/10.5281/zenodo.4618262>³³

This project contains the following underlying data:

- Data extracted from Huang *et al.*⁷ (“41467_2020_18450_MOESM7_ESM-1.csv”)

GNU General Public License v3.0.

Extended data

Zenodo: Extended data: Estimating the duration of seropositivity of human seasonal coronaviruses using seroprevalence studies. <https://doi.org/10.5281/zenodo.4566014>²⁵.

This project contains the following extended data

- SupplementaryMaterial.pdf
- Sensitivity analysis: Less informed priors for FOI (supplementary Table 1 and Figure 1)
- Sensitivity analysis: Waning estimated by strain (supplementary Table 2)
- Sensitivity analysis: Alpha and cut-off jointly simultaneously by study (supplementary Table 3 and Figure 2)
- Reverse catalytic model (supplementary Figure 3 and Table 4)
- Sensitivity analysis: Including the youngest age groups (<1 year) (supplementary Table 5 and Figure 4)
- Sensitivity analysis: Refitting the model using data from only two strains (supplementary Table 6)

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

Software availability

Source code available from: <https://github.com/erees/seasonalHCoV>

Archived source code at time of publication: <https://doi.org/10.5281/zenodo.4618262>³³

License: GNU General Public License v3.0.

Acknowledgements

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Hamish P Gibbs, Alicia Rosello, Nicholas G. Davies, Kevin van Zandvoort, Timothy W Russell, Graham Medley, Damien C Tully, Sebastian Funk, Emilie Finch, Kaja Abbas, Fiona Yueqian Sun, Rosanna C Barnard, Matthew Quaife, Oliver Brady, Joel Hellewell, David Hodgson, Carl A B Pearson, W John Edmunds, Simon R Procter, William Waite, Billy J Quilty, Jiayao Lei, James D Munday, Kathleen O'Reilly, Rosalind M Eggo, Christopher I Jarvis, Fabienne Krauer, Mihaly Koltai, Sophie R Meakin, Mark Jit, Anna M Foss, Yalda Jafari, Nikos I Bosse, Emily S Nightingale, Katherine E. Atkins. Thibaut Jombart, Frank G Sandmann, Samuel Clifford, Petra Klepac, Stefan Flasche, C Julian Villabona-Arenas, Yung-Wai Desmond Chan, Yang Liu, Kiesha Prem, Sam Abbott, Akira Endo, Amy Gimma, Gwenan M Knight

CMMID COVID-19 working group funding statements:

Hamish P Gibbs (EDCTP2: RIA2020EF-2983-CSIGN, UK DHSC/UK Aid/NIHR: PR-OD-1017-20001), Alicia Rosello (NIHR: PR-OD-1017-20002), Nicholas G. Davies (UKRI Research England, NIHR: NIHR200929, UK MRC: MC_PC_19065), Kevin van Zandvoort (Elrha R2HC/UK FCDO/Wellcome Trust/NIHR, FCDO/Wellcome Trust: Epidemic Preparedness Coronavirus research programme 221303/Z/20/Z), Timothy W Russell (Wellcome Trust: 206250/Z/17/Z), Graham Medley (B&MGF: NTD Modelling Consortium OPP1184344), Sebastian Funk, (Wellcome Trust: 210758/Z/18/Z), Emilie Finch (MRC: MR/N013638/1), Kaja Abbas (BMGF: INV-016832; OPP1157270), Fiona Yueqian Sun (NIHR: 16/137/109), Rosanna C Barnard (European Commission: 101003688), Matthew Quaife

(ERC Starting Grant: #757699, B&MGF: INV-001754), Oliver Brady (Wellcome Trust: 206471/Z/17/Z), Joel Hellewell (Wellcome Trust: 210758/Z/18/Z), David Hodgson (NIHR: 1R01AI141534-01A1), Carl A B Pearson (B&MGF: NTD Modelling Consortium OPP1184344, FCDO/Wellcome Trust: Epidemic Preparedness Coronavirus research programme 221303/Z/20/Z), W John Edmunds (European Commission: 101003688, UK MRC: MC_PC_19065, NIHR: PR-OD-1017-20002), Simon R Procter (B&MGF: INV-016832), William Waite (MRC: MR/V027956/1), Billy J Quilty (NIHR: 16/137/109, NIHR: 16/136/46, B&MGF: OPP1139859), Jiayao Lei (B&MGF: INV-003174), James D Munday (Wellcome Trust: 210758/Z/18/Z), Kathleen O'Reilly (B&MGF: OPP1191821), Rosalind M Eggo (HDR UK: MR/S003975/1, UK MRC: MC_PC_19065, NIHR: NIHR200908), Christopher I Jarvis (Global Challenges Research Fund: ES/P010873/1), Fabienne Krauer (Innovation Fund: 01VSF18015, Wellcome Trust: UNS110424), Mihaly Koltai (Wellcome Trust: 221303/Z/20/Z), Sophie R Meakin (Wellcome Trust: 210758/Z/18/Z), Mark Jit (B&MGF: INV-003174, NIHR: 16/137/109, NIHR: NIHR200929, European Commission: 101003688), Yalda Jafari (UKRI: MR/V028456/1), Nikos I Bosse (HPRU: NIHR200908), Emily S Nightingale (B&MGF: OPP1183986), Katherine E. Atkins (ERC: SG 757688),

Thibaut Jombart (Global Challenges Research Fund: ES/P010873/1, UK Public Health Rapid Support Team, NIHR: Health Protection Research Unit for Modelling Methodology HPRU-2012-10096, UK MRC: MC_PC_19065), Frank G Sandmann (NIHR: NIHR200929), Samuel Clifford (Wellcome Trust: 208812/Z/17/Z, UK MRC: MC_PC_19065), Petra Klepac (Royal Society: RP\EA\180004, European Commission: 101003688), Stefan Flasche (Wellcome Trust: 208812/Z/17/Z), C Julian Villabona-Arenas (ERC: SG 757688), Yang Liu (B&MGF: INV-003174, NIHR: 16/137/109, European Commission: 101003688, UK MRC: MC_PC_19065), Kiesha Prem (B&MGF: INV-003174, European Commission: 101003688), Sam Abbott (Wellcome Trust: 210758/Z/18/Z), Akira Endo (Nakajima Foundation), Amy Gimma (European Commission: 101003688), Gwenan M Knight (UK MRC: MR/P014658/1)

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Current Peer Review Status: ? ✓ ?

Version 1

Reviewer Report 14 October 2021

<https://doi.org/10.21956/wellcomeopenres.18416.r46084>

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Rees *et al.* provide estimations for the force of infection (FOI) and seropositivity waning rate regarding four different human coronaviruses (HCoV) strains using reverse catalytic model with age-varying FOI. The limitations of the modelling approach as well as the limitations about the datasets are well discussed.

Some minor points that should be addressed:

1. The authors give in the introduction examples about pathogens which are 'fully immunising' like pertussis. To my knowledge pertussis natural infection protects longer than vaccination but not lifelong (see Wendelboe *et al.*, 2005¹). Please rephrase the sentence accordingly.
2. Please clarify in the method section what is meant with "[...] were excluded, as well as studies with small number of data points." Is 'small number' referring to number of different age (groups) reported in the study or number of total observations in a study, and what is 'small'?
3. The full dataset used is not available on Zenodo (reference 25) but on GitHub (reference 33) [Method section, 1st paragraph, last sentence] – please check throughout the text those two references (e.g. last sentence Method section GitHub is mentioned with reference number 25).
4. In the method section it is stated that for the age at the cut-off time (a_0) also uniform priors from 0 to 5 years are also investigated, however, I don't see this prior appearing in the Table 2 with the different models and priors or in the Result section.
5. Can the authors clarify in the discussion why they did not investigate a sensitivity analysis about the different assays used in the studies, e.g. allowing to vary waning according to assays used?

6. It is not clear which model was used to produce Figure 3B and which FOI estimates were used (from the main model, all models?) and how they were pooled. The description and interpretation of Figure 3B should be deepened.

Some minor points which could improve readability:

1. In the 3rd paragraph of the introduction, the authors provide the number of observations for the studies mentioned in this paragraph except for the studies conducted in Kenya and in New York. It would help to put the results in perspective to also have the numbers for those two studies.
2. Assay description: Table 1 indicates a very rough description of the assay used in the study. For interested readers it would be helpful to have more information in the supplementary material about the assays like exact assay name, was it qualitative/quantitative, sensitivity/specificity, what cut-off values were used, what is the lower limit of detection (LLOD), what happened with equivocal results (count towards being positive or negative), etc.
3. Referring to tables and figures in the supplementary material: change 'extended data Figure 1, Table 1' to 'Supplementary Figure 1, Table 1' etc.
4. Table 1-4: add the abbreviations used within the table in the table legend (e.g. Table 1 HCoV).
5. Table 2 - 5th model: maybe rephrase 'using all data' to 'using also data on <1 year'.
6. Table 3: I would suggest to extend the column titles a bit: "FOI": clarifying that it is the one for the younger age group (i.e. lambda1); "Cut-off": clarifying that this is about splitting observations into two age groups and adding the unit years.
7. Table 4: Why are not all models from Table 2 reappearing in this table?

References

1. Wendelboe AM, Van Rie A, Salmaso S, Englund JA: Duration of immunity against pertussis after natural infection or vaccination. *Pediatr Infect Dis J*. 2005; **24** (5 Suppl): S58-61 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease modeling, biostatistics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 12 October 2021

<https://doi.org/10.21956/wellcomeopenres.18416.r46089>

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Barnaby Flower 

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Rees *et al.* provide a timely analysis of duration of natural immunity against seasonal human coronaviruses. They use an age-structured catalytic model which inputs historical seroprevalence data from five studies to estimate likely duration of seropositivity following seroconversion. They estimate HCoV antibodies last between 0.9 and 3.8 years, and find that the rate at which susceptible individuals acquire infection and seroconvert is higher in older children (>8.49 years) and adults than it is in younger children. The duration of seropositivity is consistent with previous estimates by Edridge *et al.* and tallies with emerging data concerning SARS-CoV2.

I am not a modeler and defer to my modeling colleague's review regarding aspects of the methodology. However to the non-specialist the methods appear robust and reproducible and they are transparently described in this well-written paper.

As with all models, the outputs are only as good as the inputs, and in this case, data has been extracted from just 5 studies performed between 1965 and 2011 in four countries (Hong Kong, China, USA and Germany). The studies employ different assays, namely: enzyme-linked immunosorbent assays (ELISA), immunofluorescence assays (IFA), western blots, and complement fixation (CF), hemagglutination inhibition assays (HAI) and neutralisation assays which have different sensitivities and specificities, and I suspect this will lead to heterogeneous under-

estimation of actual antibody positivity rates, particularly in comparison to current estimates of SARSCoV2 using highly sensitive ELISAs. The study would be strengthened by assay specific sensitivity analysis.

The second limitation regards not accounting for seasonality. The authors point out that other studies have found that ignoring seasonality may overemphasize the role of adults in the transmission. Given that HCoVs are detected at much higher rates in the winter and spring seasons this makes it difficult to interpret one of the study's major findings of a higher force of infection in adults. This is mentioned in the 4th paragraph of the discussion but not in the context of the finding that the FOI was estimated to be twice as high in the older age group (6th paragraph) and perhaps this should be better tied together.

While these considerations might improve the paper, the limitations are well discussed and the manuscript is well worthy of indexing and dissemination.

One minor point:

In paragraph 4 of the methods it says:

"There is little information on the attack rate of HCoVs, but there have been several systematic reviews and meta-analyses looking at unvaccinated individuals which have reported the attack rate to range between 15.2% – 22.5% in children and 3.5% – 10.7% in adults^{26–28}."

This sentence is missing 'influenza'.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

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Yes

If applicable, is the statistical analysis and its interpretation appropriate?

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Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: SARSCoV2 antibody seroprevalence, SARSCoV2 diagnostics, Hepatitis C Clinical Trialist. No modeling expertise.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 28 June 2021

<https://doi.org/10.21956/wellcomeopenres.18416.r44311>

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**Angkana T. Huang**

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Leveraging data on other human coronaviruses (HCoV) that have been circulating for longer, the authors estimated a range of antibody waning rates that might apply to SARS-CoV-2. They performed multiple sensitivity analyses to assess the robustness of their estimates. Their results also pointed towards transmission being higher in older individuals.

The authors provided ample background to understand the motivation and the approach of their work. Below are some minor points that I view should be addressed.

1) Please consider using the term 'seropositivity waning rate' instead of 'immunity waning rate' for ω as many of the assays in the dataset are binding assays which may not directly translate to protection, though correlated.

2) I appreciate that the authors included multiple sensitivity analyses in their study. I would like to suggest one more where waning rates are assay specific. The assays measure different functional aspects of the antibodies which may involve different subsets of the induced repertoires. Some hints exist in the authors' results. Shao (2007) and Chan (2009) used IgG ELISA while Monto (1974) and Sarateanu (1980) were HI based. Looking at plots of the observed data, these tend to exhibit more prominent wanes. In Table S6, Model 1, 5, and 6 where Monto (1974) and Sarateanu (1980) were included, the estimated waning rates were much higher than the others. It could be that these were specific to HCoV-OC43, but looking at Table S2, the estimates for -NL63 and -HKU1 were similar to -OC43 (considering both the point estimates and credible intervals). Posterior density plots from code provided by the authors showed that combined cutoff of the Cavallaro (1970) and the Monto (1974) study in the main model, though converged, is bimodal. I wonder if this resulted from the model trying to accommodate the enforced single waning rate between studies which used different assays. This assessment will likely help the field reconcile discrepancies in serosurveys that were measured using different assays.

3) As the authors pointed out, data for some strains were from the same settings. This is evidence for co-circulation. The cross-reactivity between strains, specifically within alpha- and beta-CoVs, would affect the seropositivity. I acknowledge that literature is slim on what the degree of cross-reactivity is and the limited data may make it hard to infer from the data. Anyhow, please consider adding some discussion around how this would change the estimated waning rate as it will help readers adjust their expectations on what the true waning rates could be. One way to gain such intuition may involve extending the models to include cross-reactivity in studies with known co-

circulation, imposing different sets of informative priors to the cross-reactivity rate, and assess how those affect the inferred waning rates. It is optional whether the authors would take on this path.

4) The authors may consider additional metrics of model performance, for instance, the expected log predictive density (ELPD) which is based on approximate leave-one-out cross-validation, <https://doi.org/10.1007/s11222-016-9696-4>. The measure provides uncertainties around the performance estimates which may help determine the superiority among the suite of models, especially for ones where DIC were very similar.

5) It would be helpful to provide an equation to explicitly show the link between the estimated waning rates and the duration of antibody persistence which were reported throughout the paper, and is the main finding of the study.

6) In contrast to the previous point, the authors provided an equation linking the FOI to the attack rates but barely touched upon this topic in the paper except for one occurrence in the Discussion. May there be ideas that the authors wished to discuss but were not fully expressed in the text?

7) It is unclear what the motivation for the analysis which led to Figure 3 was. Providing some context, especially how that would better our projections on SARS-CoV-2 would be helpful.

8) Lastly, there are some truncated sentences or missing/inconsistent information in the paper that needs to be fixed. For example:

- In the Methods, “The different assays used in each study for the different strains is shown, and where the antibody detected was specified this is included in the table.”
- In the Results, “When the relative change in FOI and cut-off parameters were simultaneously estimated by setting (extended data Figure 2, Table 3) the duration of antibody persistence was estimated to be shorter, ...”.
- According to the captions, it occurs to me that the pairings are as follows: Table S1 with Figure S1, Table S3 with Figure S2, Table S5 with Figure S4. The pair of Table S2 is not obvious. It is unclear for Figure S3 which analysis this belongs to. Please also double check that the Extended data section in the main text matches the materials provided in the supplement.
- “The inference was impleented in Rjags...”
- The figure legend of Figure 3A says “reverse catalytic & age varying FOI” while the caption says “reverse catalytic model with time-varying FOI”. The colors also do not seem to match the legend (blue vs green vs grey). May be helpful to choose colors that are more different, especially that the lines in the legend keys are quite thin.
- It is unclear which model was used to generate Figure 3B. I am guessing the “reverse catalytic model” from its matching color but explicit statements would be helpful to the readers.
- Please consider breaking this portion in the Discussion into a new sentence, “... and a meta-analysis of contact tracing studies found that children had 56% (31% – 71%) lower odds of

becoming an infected contact compared with adults⁵².”

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Reviewer Expertise: infectious disease modeling

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